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Searching for the principles of brain plasticity and behavior

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ABSTRACT

An important development in behavioral neuroscience in the past 25 years has been the demonstration that the brain is far more flexible in structure and function than was previously believed. Studies of laboratory animals have provided an important tool for understanding the nature of brain plasticity and behavior at many levels ranging from detailed behavioral paradigms, electrophysiology, neuronal morphology, protein chemistry, and epigenetics. Here we seek a synthesis of the multidisciplinary work on brain plasticity and behavior to identify some general principles on how the brain changes in response to a wide range of experiences over the lifetime.

1. Introduction

Although the idea that experience can modify brain structure is not new (e.g., Ramony Cajal, 1928) evidence demonstrating what changes occur and why they occur has really only become available in the past 25 years. There is now an extensive literature correlating neuronal and other changes with behavioral changes in species as diverse as insects and humans. Our goal here is to identify some general principles of brain plasticity and behavior and to summarize the factors that best illustrate the relationship between brain plasticity and behavior in mammals.

2. Assumptions

As we search for the principles of brain plasticity, we will make three fundamental assumptions. First, we assume that changes in the structure or operation of the brain will be correlated with behavioral changes. The primary function of the brain is to produce behavior but behavior is constantly changing. Although minute-to-minute changes in behavior, such as changing one's mind about choices for dinner, likely do not reflect meaningful brain changes, plastic changes related to behavior can be both short-term as well as long-term. For example, some memories are relevant only for the next few minutes whereas others may be important for years (e.g., Tetzlaff, Kolodziejski, Markelic, & Worgotter, 2011). Although the details of what synaptic changes might occur at different time scales are poorly understood, single neurons can show persisting changes in postsynaptic potentials or firing rates that could underlie brief memories. In contrast, long-lasting memories likely result from structural changes such as the growth of new synapses and associated neural networks. Both types of plastic changes are associated with behavioral changes but in quite different ways.

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Second, changes in the brain can be shown at many levels of analysis as summarized in Table 1. The choice of level will depend upon the question being posed and the species being studied. For example, if a researcher is interested in brain changes associated with skilled motor learning in people, the level might be neural imaging, possibly to identify motor maps. In contrast, if the question is related to motor learning in a laboratory animal, the level could be invasive such as cellular recording or postmortem measures of neuronal morphology. There is no "correct" or "best" level. Studies need to be done at many levels to thoroughly understand brain plasticity and behavior. But we must be wary of being too reductionistic. Understanding the operation of calcium channels may be very important for developing drugs to facilitate recovery from brain injury but is not going to be too helpful in understanding how we generate language.

Third, although correlation does not demonstrate causation, behavioral neuroscience is, by its nature, correlational. Some behavior–brain correlations likely do reflect causation whereas others are more ambiguous. Consider an example. If we give an animal a psychoactive drug, which produces symptoms of Parkinson's disease within hours, the brain changes induced by the drug can be presumed to be the cause of the behavioral changes. But, if we do the same study and measure changes in synaptic organization in the striatum several days later, we cannot be certain what caused what. We can conclude that the drug changed the brain and behavior, but it is less clear that the drug directly caused the neuronal changes in the striatum or that the neuronal changes are related to the behavioral changes. Or, they may both be related to some other change in the brain that was caused by the drug. This ambiguity in causal relationships often leads to the criticism that studying brain plasticity and behavior is really "only studying correlations". This may be true but this is not a reason to dismiss the studies. Given our current general ignorance over the principles of brain plasticity we believe that some level of ambiguity will be inevitable.

3. General principles of plasticity

It is, of course, presumptuous for us to claim to understand the general principles of brain plasticity when so little is known about the fundamental phenomena at play. Nonetheless, we believe that the time is right to reflect on what is known and try to identify some of the "rules". These rules should be seen as a work in progress that hopefully will provide a framework for progress.

Table 1 – Levels of analysis.

1. Behavior
2. Neural imaging
3. Maps – invasive and noninvasive
4. Physiology (e.g., LTP, unit recording)
5. Neuronal morphology
6. Genetics and epigenetics
7. Proteins and other molecules

3.1. *Plasticity is found in all nervous systems and the principles are conserved*

Although most current work on brain plasticity is conducted on mammals, many of the early ideas regarding plasticity came from the study of invertebrates (e.g., Bailey & Kandel, 2008) and other nonmammals, such as birds (e.g., Horn, 2004). We now know that all animals, including very simple ones like *Caenorhabditis elegans*, can show various forms of learning, which is correlated with neuronal plasticity (e.g., Ardiel & Rankin, 2010). This plasticity includes both pre- and postsynaptic changes that are remarkably similar to those observed in animals with much more complex nervous systems. There are certainly differences in the details, such as the nature of gene expression changes and changes in second messengers, but the general principles appear to be conserved across diverse phyla. The conservation of principles allows researchers to use a wide range of models to search for the neural mechanisms of plasticity in humans.

3.2. *The primary form of plasticity is a change in neuronal network organization*

We have noted that plasticity can be studied at many levels, but an overriding principle is that behavioral change is related to specific gain and elimination of synapses within ensembles of connections (e.g., Caroni, Donato, & Muller, 2012). The cause of the synaptic change is ultimately related to gene expression and related molecular events, but it is the synaptic change that is most related to behavior. One common erroneous assumption is that positive behavioral change, such as learning, is related to adding synapses whereas negative behavioral change, such as that related to stress, is related to losing synapses. In fact, most behavioral change is related to both the addition and the subtraction of synapses within a network of neurons. One exception may be the neuronal changes related to dementia, which are likely mostly synaptic loss.

3.3. *There are three general types of plasticity*

Three types of plasticity can be distinguished in the normal brain: experience-expectant, experience-dependent, and experience-independent (Black, Greenough, & Wallace 1997; Shatz, 1992). *Experience-expectant* plasticity largely occurs during development. For different brain systems to develop they require specific types of experience. A good example is the development of ocular dominance columns found in the primary visual cortex. These alternating columns provide a mechanism for the inputs from the left and right eyes to be combined to produce binocular vision. Wiesel and Hubel (1963) showed that if one eye is kept closed after birth in kittens, the open eye expands its territory leading to shrinkage of the column related to the closed eye. When the closed eye is eventually opened, its' vision is compromised.

Experience-independent plasticity is also largely a developmental process. It is impractical for the genome to specify the connectivity of every connection in development. Instead, the brain is designed to produce a rough structure in which there is an overproduction of neurons, and later, connections, that

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